sequence encoding IEF SSP 9502 and its translation as SEQ ID NO: 47 and SEQ ID NO: 48, respectively. Basis for the amendment to the Sequence Listing can be found, for example, in the Specification and in Honore *et al.* (1994) *Gene* **151**: 291-196, the disclosure of which is incorporated by reference into the Specification (see page 7, lines 14-15 of the Specification, and page 292 of Honore *et al.*, a copy of which was provided as reference CO with the Information Disclosure Statement of May 17, 1999). Similarly, the Specification is herein amended to make reference to SEQ ID NO: 47 and SEQ ID NO: 48. Applicants believe that the amendment introduces no new matter.

A computer-readable copy of the substitute Sequence Listing is also provided. The content of the computer readable form of the Sequence Listing is the same as the enclosed paper copy of the Sequence Listing.

Claim 24 has been amended to recite a method comprising detecting a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 47 or a sequence complementary thereto. Support for the amendment can be found throughout the Specification and at least at page 10, lines 18-19; at page 11, lines 7-29; at pages 23-25; at pages 46-47; in the paragraph bridging pages 51 and 52; in claims 24 and 25 as originally-filed, and at page 292 of Honore *et al.* (1994) *supra.*

Claim 25 has been amended to recite a binding moiety comprising a detectable label and to correct claim dependency. Support for the amendment to claim 25 can be found throughout the Specification and at least at page 9, lines 15-17, and at page 24, lines 4-6.

Claims 50-52 have been amended to correct antecedent basis.

Support for new claim 55 can be found throughout the Specification and at least at page 11, lines 7-29; at pages 23-25; at pages 46-47; in the paragraph bridging pages 51 and 52; in claims 24 and 25 as originally-filed, and at page 292 of Honore *et al.* (1994) *supra.* Support for new claims 56, 59, and 60 can be found throughout the Specification and at least at page 23, lines 25-26. Support for new claims 57 and

58 can be found throughout the Specification and at least in the sentence bridging pages 23 and 24. Support for new claim 61 can be found throughout the Specification and at least in the paragraph bridging pages 24 and 25. Support for new claim 62 can be found throughout the Specification and at least at page 10, lines 18-19; at page 11, lines 7-29; at pages 23-25; at pages 46-47; in the paragraph bridging pages 51 and 52; in claims 24 and 25 as originally-filed, and at page 292 of Honore *et al.* (1994) *supra*. Support for new claim 63 can be found throughout the Specification and at least at page 23, lines 26-27.

In accordance with 37 C.F.R. § 1.121, Applicants enclose a copy of a marked-up version of the amended claims and of the amended paragraph of the Specification, showing the changes in the text. Applicants believe that the amendments introduce no new matter.

Applicants respond to each rejection in the order in which it appears in the Office Action.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph: Written Description

According to section four of the Office Action, claims 24-25 and 39-54 presently stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action alleges that many molecules may encode the amino acid residues of SEQ ID NO: 10 and that Applicants were not in possession of methods of using all of the molecules for detecting cancer at the time the application was filed. Applicants traverse this rejection to the extent it is maintained over the pending claims as amended.

Claims 39-49 and 53 have been cancelled, obviating the rejection of these claims. Pending claims 24 and 54, as amended, are directed to a method comprising detecting a nucleic acid molecule comprising the nucleotide sequence set forth in

SEQ ID NO: 47 or a sequence complementary thereto. Similarly, claims 25, 50-52, and 55-61 are drawn to a method using a binding moiety capable of binding specifically SEQ ID NO: 47 or its complement. New claims 62 and 63 are drawn to a method comprising detecting a nucleic acid molecule that specifically binds a sequence complementary to SEQ ID NO: 47 or that hybridizes to a sequence complementary to SEQ ID NO: 47 under defined conditions. Applicants submit that the subject matter of the pending claims is described in the Specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed, and respectfully request that this rejection be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement

According to section five of the Office Action, claims 24-25 and 39-54 presently stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that the Specification "merely correlate[s] detection of polypeptides to . . . cancer", "fails to test or determine if the nucleic acid molecules encoding those polypeptides also correspond to cancer, and . . . fails to address that many of the nucleic acid molecules which might encode the [polypeptides] would likely not even exist in the . . . samples." Applicants traverse this rejection to the extent it is maintained over the pending claims as amended.

As a preliminary matter, Applicants note that, as amended, claims 24 and 53-54 are directed to a method comprising detecting a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 47, or a sequence complementary thereto; claims 25, 50-52, and 55-61 are drawn to a method using a binding moiety capable of specifically binding to SEQ ID NO: 47 or its complement; claims 63 and 64 are drawn to a method comprising detecting a nucleic acid molecule that specifically binds a sequence complementary to SEQ ID NO: 47 or that hybridizes to

a sequence complementary to SEQ ID NO: 47 under defined conditions. Applicants submit that the currently pending claims recite nucleotide sequences and binding moieties specifically related to SEQ ID NO: 47. Accordingly, Applicants submit that the foregoing claim amendments obviate the suggestion in the Office Action that the Specification "fails to address that many of the nucleic acid molecules which might encode the [polypeptides] would likely not even exist in the . . . samples." Furthermore, Applicants submit that the discussion in the Office Action of the predictability of protein function where "substitutions or fragments of nucleic acids are used" is irrelevant to the claims, as amended; the amended claims relate to detection of a nucleic acid, not to a particular protein function.

Applicants submit that the Specification clearly describes the invention and the manner in which it can be carried out (see, e.g., pages 23-25). Applicants submit that practice of the claimed invention would not require undue experimentation. The Office Action acknowledges that "[t]he specification teaches detecting cervical cancer by detecting the presence of a polypeptide or specific fragments thereof," but argues that protein expression levels do not *necessarily* correlate to nucleic acid levels. In support of this argument, the Office Action cites Alberts *et al.*, Molecular Biology of the Cell, 3rd edition, 1994, pages 403-404, 429-437, and 444-465 of which are attached as Exhibit A.

Applicants submit that Alberts *et al.* teaches that eukaryotic protein expression is routinely regulated at the nucleic acid level. See, e.g., page 403: "for most genes transcriptional controls are paramount"; and page 453: "controls on the initiation of gene transcription are the predominant form of regulation for most genes." For example, at pages 429-430 and 436-437, Alberts *et al.* discusses the human β-globin gene and the "complex array of gene regulatory proteins" that modulate the transcription of β-globin during human development such that "the ε-globin gene is expressed in the embryonic yolk sac, γ in the yolk sac and the fetal liver, and δ and β primarily in the adult bone marrow." At pages 444-445, Alberts *et al.* teaches that, whereas in proliferating muscle precursor cells "muscle-specific

proteins and their mRNAs are absent or are present in very low concentrations", as the cells differentiate "the corresponding genes are all switched on coordinately", a process requiring transcriptional regulatory factors such as myogenin. Generally, transcriptional control may be exerted through the action of transcription factors that associate with the DNA, as in β-globin and in muscle differentiation, through chromatin structure, as in β-globin and in X chromosome activation (see pages 446-448) and/or through DNA methylation, as in the muscle-specific actin gene (p.450) and in IGF-2 (p.451).

Furthermore, Applicants submit that the claims, as amended, do not require transcriptional regulation of a target nucleic acid. For example, the Office Action cites the transferrin receptor as an example of posttranslational regulation: transferrin receptor mRNA is degraded in the presence of excess iron. If a target nucleic acid is degraded, Applicants submit that the change in mRNA levels or the rate of degradation could be detected in the practice of the pending claims. Similarly, Alberts *et al.* recites other forms of mRNA regulation, including transcription attenuation (p.454), alternative splicing (pp.454-455), changes in the site of RNA transcript cleavage and poly-A addition (which regulate, for example, "the switch from the synthesis of membrane-bound to secreted antibody molecules that occurs during the development of B lymphocytes"; p.456), RNA localization (pp. 458-459), and RNA editing (as in, for example, apolipoprotein-B; p.461). Applicants submit that each of these forms of regulation may cause detectable changes in the RNA. Thus, assuming *arguendo* that the level of a cervical cancer-associated protein is not regulated by transcription (unlike most genes, in which "transcriptional controls are paramount") but by one of these methods of gene regulation, Applicants submit that the nucleic acid could have a detectable property indicative of the presence of cervical cancer.

Furthermore, Applicants submit that, in cervical cancer, detectable changes in nucleic acids encoding gene products associated with cancer have been reported for a number of genes and include, for example:

Anti-apoptotic BAG-1 protein is detectable at low levels, if at all, in normal cervical tissues, but is overexpressed in most cervical carcinomas tested. (Yang et al., (1999) Exp. Cell Research, 247:200-207 and 256:583, a copy of which is attached as Exhibit B). "Overexpression [of BAG-1 is] regulated at the transcriptional level" (Id., abstract). "The expression of BAG-1 RNA correlated well with that of the BAG-1 protein . . . , suggesting that the overexpression of BAG-1 protein is caused by increased transcription of BAG-1 gene" (Id. at 202).

The serum level of ICAM-1 protein is significantly elevated in patients with advanced-cervical squamous cell carcinoma (Nasu *et al.* (1997), Gynecologic Oncology 65:304-308, a copy of which is attached as Exhibit C). Expression of ICAM-1 mRNA was observed in six of seven cervical squamous cell carcinoma tissues, but was not detected in four samples of normal cervical tissue (Id. at 305).

Variant CD44 synthesis is enhanced in uterine cervical carcinomas, based on immunostaining and PCR (Dall *et al.* (1994), Cancer Research 54:3337-3341, a copy of which is attached as Exhibit D). Moreover, "cervical carcinomas appear to demonstrate . . . a change of splice pattern leading to the acquisition of a new (transition) epitope" (Id. at 3340). "Fifteen of 16 [cervical] cancer samples were stained strongly with an antibody" recognizing that epitope, which was not detectable in normal cervical epithelium (Id., abstract).

Upregulation of telomerase activity occurs more frequently in higher-grade cervical intraepithelial neoplasia and cervical cancer lesions (Wisman *et al.* (2000), Human Pathology 31(10):1304-1312, a copy of which is attached as Exhibit E). "[H]igher semiquantitative expression of hTERT," the catalytic subunit of telomerase, "as determined by rt-PCR, [is] related to higher grade of (pre)malignant cervical lesions" (Id. at 1309) and to telomerase activity levels (Id., abstract).

The gene encoding *PIK3CA*, which encodes the p110α subunit of PI 3-kinase, is amplified in some cervical carcinomas (Ma *et al.* (2000), Oncogene 19:2739-2744, a copy of which is attached as Exhibit F). "In cervical cancer cell lines harboring amplified *PIK3CA*, the expression of gene product (p110α) of *PIK3CA* was increased, and was subsequently associated with high kinase activity" (Id., abstract).

Accordingly, Applicants submit that if, "for most genes, transcriptional controls are paramount", and if nucleic acids encoding proteins upregulated in cervical cancer frequently have detectable changes, one might reasonably expect, upon reading the present Specification, that a nucleic acid related to SEQ ID NO: 47 would have a detectable property indicative of cervical cancer.

Applicants submit that the test for enablement, however, is whether persons skilled in the art can make and use the invention without undue experimentation. See MPEP 2164.01; see also MPEP 2164.02 ("lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement"). As the Office Action acknowledges, additional factors relevant to enablement include the nature of the invention and the breadth of the claims (addressed *supra* in the discussion of nucleotide sequences and binding moieties recited in the pending claims), the amount of direction or guidance presented in the Specification and the state of the prior art, the relative skill of those in the art, and the quantity of experimentation necessary to make or use the invention based on the content of the Specification.

Applicants submit that the Specification provides extensive guidance on methods for detecting, in a tissue or body fluid sample, a nucleic acid molecule encoding a cancer-associated protein, and multiple citations to prior art references with further information useful in the practice of the methods (see, e.g., pp. 23-25 of the Specification and references cited therein). Applicants further submit that the level of skill in the art at the time the application was filed was high and that minimal experimentation would be necessary to confirm that the presence of a particular nucleotide sequence in a tissue or body fluid sample is indicative of a cancer. Applicants submit that the instant application is therefore similar to the one at issue in In re Wands, 858 F.2d 731 (Fed. Cir. 1988), in which "the Court held that the Specification was enabling with respect to the claims at issue and found that 'there was considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and 'all of the methods needed to practice the invention were well known.'" MPEP 2164.01(a). Accordingly, Applicants submit that the claims are not unduly broad, that the art is not necessarily unpredictable, that the working examples in the Specification are relevant, that the teachings in the Specification regarding detecting cancer by detecting a nucleic acid are extensive, that the methods needed to practice the

invention were well known, that the level of skill in the art was high, and that any experimentation necessary to practice the claimed method would be minimal and not undue. Applicants therefore request that this rejection be reconsidered and withdrawn.

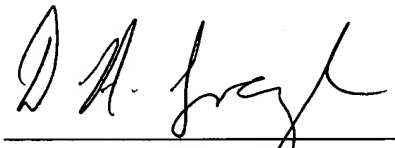
CONCLUSION

In view of the amendments to the claims and the arguments presented herein, Applicants respectfully request that the foregoing rejections be reconsidered and withdrawn.

The Examiner is invited to call the undersigned at (617) 248-7317 with any questions or comments if the Examiner believes that a telephone conversation would be helpful in expediting prosecution of the instant application. Please charge any additional fees to Attorney's Deposit Account No. 20-0531.

Early favorable action is respectfully solicited.

Respectfully submitted,



Date: July 30, 2001
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MARKED UP COPY OF THE AMENDMENTS TO THE CLAIMS AND SPECIFICATION

In the Specification:

Ten masses were detected by mass spectrometry from seven of the CvC-3H peaks. Amino acid sequence was obtained for three peptides, two by Edman degradation and one by carboxypeptidase-MALDI-TOF analysis. The sequences obtained for these peptides, shown in Table 4, match a protein known as IEF SSP 9502 or "novel human nuclear phosphoprotein" (Honore *et al.* (1994) *supra*; GenBank Accession #L07758). The nucleotide sequence of the cDNA encoding IEF SSP 9502 is shown in SEQ ID NO: 47, and the [The] complete amino acid sequence for this protein, as derived from [a]the gene sequence, is shown in [SEQ. ID No.: 10] SEQ ID NO: 10 and SEQ ID NO: 48. Seven other masses from peak fractions separated on the CvC-3H tryptic map also matched those of predicted tryptic fragments from this protein. Mass correlation data of tryptic peptides from CvC-3H are summarized in Table 4. The predicted molecular weight of the nuclear phosphoprotein, based upon its nucleotide sequence, is 55 kDa, whereas its observed molecular weight by 2-D gel analysis is 79 kDa (Honore *et al.* (1994) *supra*).

In the claims

24. (Twice Amended) A method for detecting cervical cancer in a human, the method comprising:

detecting, in a tissue or body fluid sample from the human, a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:47 or a sequence complementary thereto, [the presence of a nucleic acid molecule or a sequence complementary thereto in a tissue or body fluid sample of the human, wherein the nucleic acid molecule encodes a protein having an amino acid sequence selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, and SEQ ID NO. 10], wherein the nucleic acid molecule, if present in the sample, is indicative of the presence of cervical cancer in the human.

25. (Amended) The method of claim 55[24], wherein the binding moiety comprises a detectable label[said method comprises reacting the sample with a labeled hybridization probe capable of hybridizing specifically with at least a portion of the nucleic acid molecule].

26-49. Canceled.

50. (Amended) The method of claim 25 wherein the [labeled hybridization probe] detectable label comprises a radioisotope.

51. (Amended) The method of claim 25 wherein the [labeled hybridization probe] detectable label comprises a fluorescent compound.

52. (Amended) The method of claim 25 wherein the [labeled hybridization probe] detectable label comprises an enzyme.